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Enantioselective Cu-II-Catalyzed Diels-Alder and Michael Addition Reactions in Water Using Bio-Inspired Triazacyclophane-Based Ligands

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SUPPORTING INFORMATION

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Title: Enantioselective Cu^{II}-Catalyzed Diels–Alder and Michael Addition Reactions in Water Using Bio-Inspired Triazacyclophane-Based Ligands

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Modelling

Complexes between the TAC-ligands, copper(II) and substrate **24** were prepared in DS Viewer Pro 6.0.ⁱ Ligands around the copper centre were positioned in a square-pyramidal geometry with the imidazole ligands in the square-plane and the carbonyl oxygen atom at one of the axial positions of the copper (figure S1). Structure optimization was performed using the ‘clean structure’ command until no change in the structures was observed. This procedure was carried out for complexes between copper(II), substrate **24** and ligands **6**, **8**, **11**, **15**, and **17**.

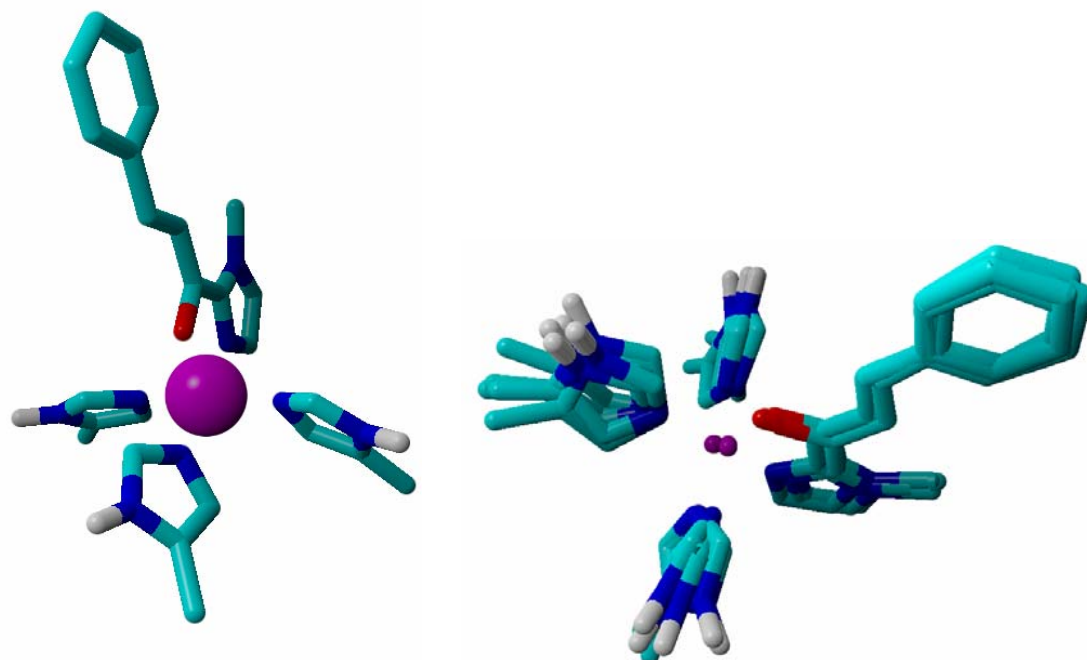


Figure S1. Geometric arrangement around the copper(II)-ion in the active site of complex **A** (left). The lower three imidazole ligands originate from the TAC-based ligands. On the right, an overlay of 5 complexes is shown.

These complexes, that were prepared with DS Viewer Pro, were then loaded into YASARAⁱⁱ (version 8.3.3) as pdb-files. After this, the simulation cell boundaries were set automatically and the Yasara2 force field was selected (the following force field terms were activated: bond, angle, dihedral, planarity, coulomb, Van der Waals). After initiation of the force field, the second substrate (cyclopentadiene (Cp) or dimethyl malonate (DMM)) was added to the soup and positioned within the simulation cell boundaries.

Then, docking of cyclopentadiene (Cp) onto complexes ^D**A**, **B**, **C**, and **D** was performed (ligands in complexes: ^D**A** = TAC(D-His-Ac)₃; complex **B** = TAC(Gly-L-His-Ac)₃; complex **C** = TAC(L-Trp-L-His-Ac)₃; complex **D** = TAC(L-His-Isovaleric amide)₃) (see figure S2 for 2D-structures of the complexes). For this, 10 docking runs with a cluster RMSD of 5.00 Å were carried out using AutoDock 4.ⁱⁱⁱ

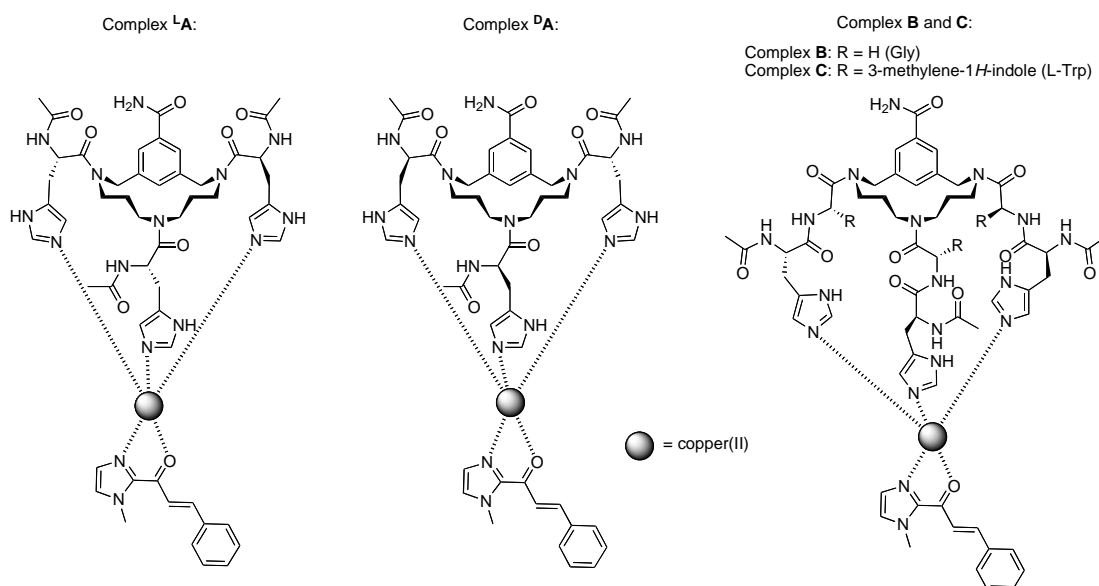


Figure S2. 2D-views of the structures of the complexes used. Complex **D** is similar to complex ^LA, with an isovaleric group instead of an acetyl group.

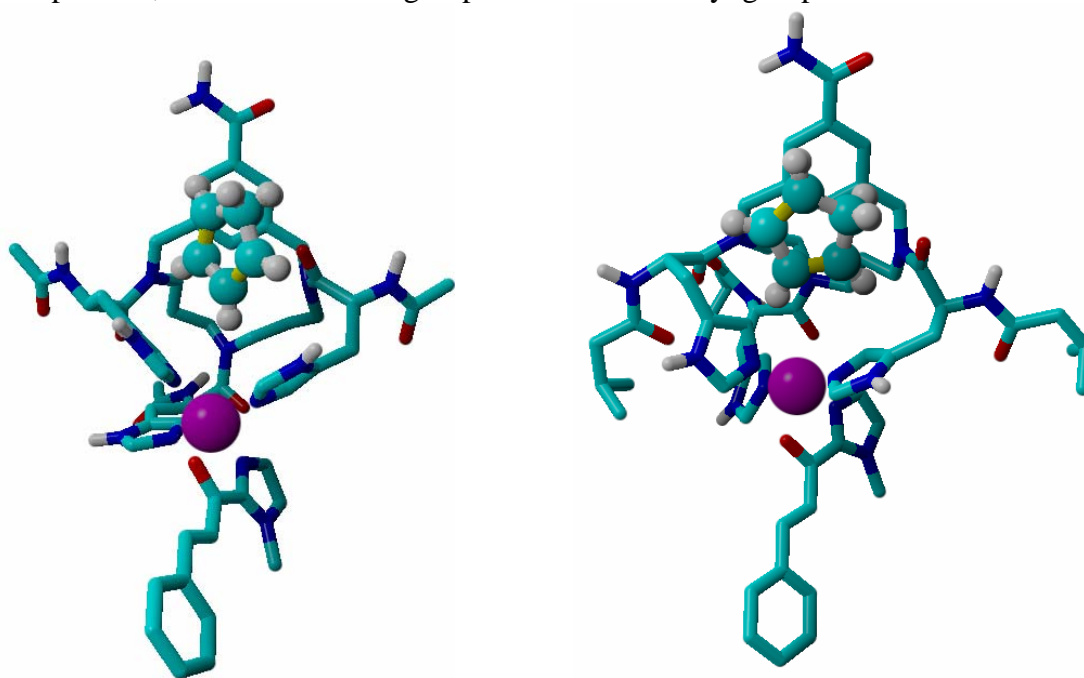


Figure S3. Result of the docking experiment of Cp onto complex **A^D** and **D**. All ten Cp-molecules are positioned close to the TAC-scaffold as well as to the catalytic site. All have the same orientation, as is evident from the methylene groups.

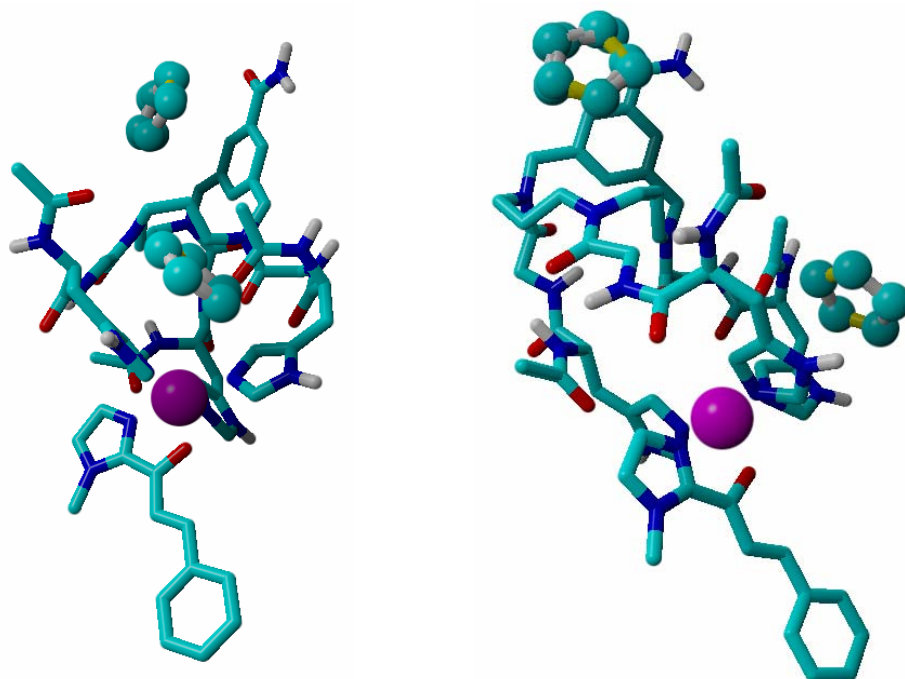


Figure S4. Two views of the result of the docking experiment of Cp onto complex **B** (with Gly-L-His-Ac attached to the TAC-scaffold). Nine Cp-molecules are positioned close to the TAC-scaffold, only one Cp-molecule is close to the catalytic site.

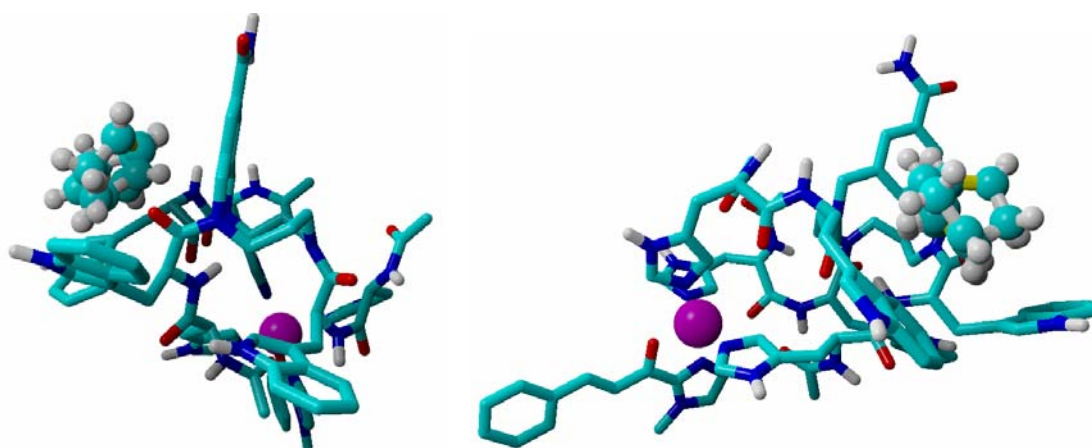


Figure S5. Two views of the result of the docking experiment of Cp onto complex **C** (with L-Trp-L-His-Ac attached to the TAC-scaffold). All ten Cp-molecules are positioned close to the TAC-scaffold away from the catalytic site.

Overlay of complex ^L**A** (gray) and ^D**A** (bleu). Chiral atoms of the histidine residues are shown as small spheres, copper(II)-ions are shown as large spheres.

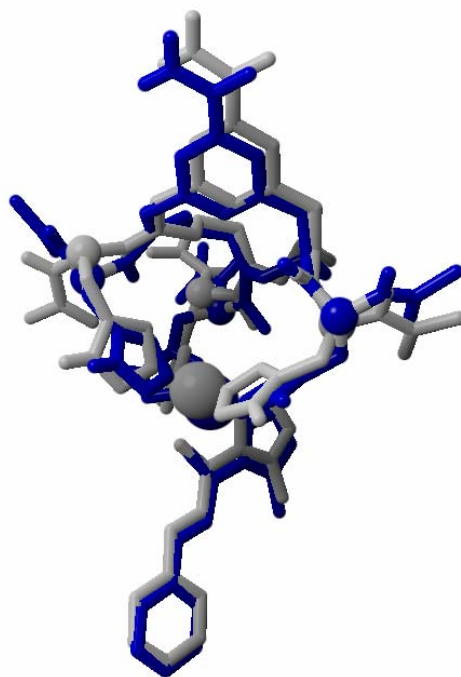


Figure S6. Overlay of complex ^DA (gray) and ^LA (blue).

Notes and References:

ⁱ Obtained as trial-version from Accelrys® (see <http://accelrys.com/products/discovery-studio/visualization.html>).

ⁱⁱ E. Krieger, G. Koraimann, G. Vriend, *Proteins: Structure, Function, and Genetics* **2002**, 47, 393-402.

ⁱⁱⁱ G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, *J. Comput. Chem.* **1998**, 19, 1639-1662.